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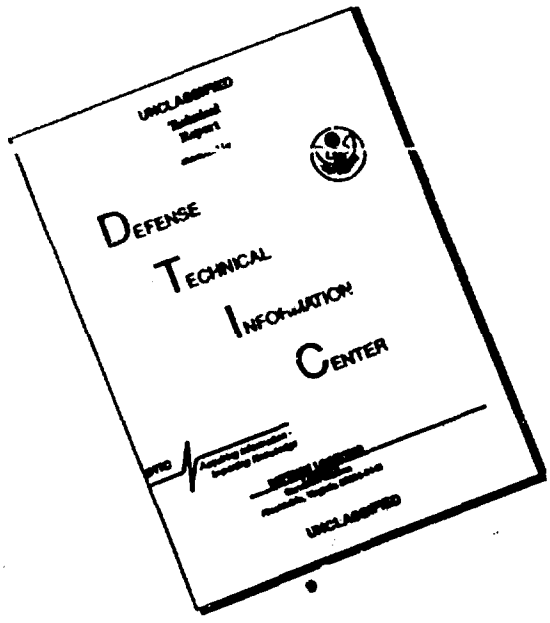

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13. ABSTRACT *(Maximum 200 words)*

HIV causes a persistent infection that results in AIDS, a major health to military and civilian populations we have and continue to study both arms of the immune system -- one that produces antibodies and one that makes cytotoxic T lymphocytes (CTL). Our purpose is two-fold. First, to determine which is important, or more essential, in producing immunity. This data should be essential for vaccine production to that end we have evaluated CTL activity in selected patients from the onset of HIV infection and through their clinical course. Second, to determine the role of antibody and/or CTL in contributing the disease. Toward that end we have defined, in three separate HIV-1 infected individuals, monoclonal antibodies that react with gp41 aa644-663, but also binds to a novel antigenic determinant on mammalian astrocytes.

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PI Signature Michael B. A Oldstone, MD Date 8 July 93

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Final Scientific Report
Army Contract Number DAMD17-90-C-0070
Principal Investigator: Michael B. A. Oldstone, M.D.

I. Introduction/Overview

The molecular anatomy of the HIV-1 genome and its replicative strategy is well known. By contrast how the virus causes disease is poorly understood. Similarly, which of the two arms of the immune system -- the one that produces antibodies or the one that generates cytotoxic T lymphocytes (CTL) -- is more important in producing vaccine induced immunity, is not clear. In addition to their protective role, antibodies and CTL also contribute to disease in several viral infections. To that end, we studied in selected HIV-1 patients the generation of monoclonal antibodies to HIV-1 gp41 that also bound to mammalian astrocytes. Using competitive inhibition assay we noted that all three monoclonal antibodies studied bound to gp41 amino acid (aa) sequence 644-663. These results record molecular mimicry between a novel astrocyte antigen and a gp41 structural protein. Further, they document that an antibody response generated in some HIV-1 infected individuals is able to bind to self antigen or astrocytes. Additionally, we analyzed CTL in HIV-1 infected individuals. In four individual patients we charted the generation of CTL from the onset of infection, prior to the generation of neutralizing antibodies, during the course of their infection. The highest CTL response was to envelope (ENV) with responses to GAG, POL, and NEF occurring later during the course of infection. CTL ENV response was associated with the decrease in viral load during the initial phase of viral infection. In two patients, a decrease in CTL response occurred several months later. The correlation of this diminished response with enhanced viral load and antibody titers to the patient's viral isolate is currently under study.

The first half of support (Mid-Term Report) continued our studies to define and fine map the immunodominant domain of HIV-1 and HIV-2 for B cell (antibody) responses. Utilizing synthesized peptides and several raised murine monoclonal antibodies, the minimal essential epitope was found to consist of 7 aa peptide: aa603-609, HIV-1; aa597-603, HIV-2 -- both containing flanking cysteine residues. Thus, during the first half of support we documented the essential contribution of the flanking cysteines and solved the two-dimensional structure of this B cell epitope using NMR. Of murine monoclonal antibodies raised to HIV-1 gp41 aa598-609, a few (7 of 51) also reacted with a novel astrocyte antigen. Conditions in which this novel antigen was expressed and the topographic areas in the brain where the greatest expression occurred was determined. Three expression libraries were constructed, but despite screening $\sim 6 \times 10^6$ plaques from each library, we were unable to enhance for and isolate the gene that encoded the novel astrocyte antigen mimicking HIV-1 gp41 segment. CTL responses to HIV were undertaken and two novel CTL epitopes mapped. Further, conditions for analyzing peripheral blood mononuclear samples harvested and to be harvested for CTL activity, from the six patients being evaluated from onset of disease until AIDS, were established.

II. Specific Accomplishments

a) Molecular Mimicry Accompanying HIV-1 Iinfection -- Human Monoclonal Antibodies that Bind to GP41 and to Astrocytes

Nine human monoclonal antibodies that reacted with HIV-1 gp160 were obtained and studied. Three monoclonal antibodies from three different individuals were found to bind to HIV-1 gp41 and also cross-reacted with mammalian astrocytes. (Table 1).

Table I
Monoclonal Antibodies Raised During HIV-I Infection that Bind to HIV-1 gp41 but also Cross-React with Astrocytes

Monoclonal Antibody	Source	Species	Characteristics	Binds to (protein)	HIV Reactivity to gp41 Sequence	Cross-Reacts with Reactive Astrocytes
M22*	MBAO	Mouse	Raised by immunization with peptie, IgG1 Ab	gp41	aa603-609	+ + +
15G1	ND	Human	Raised during infection, IgG2 Ab	gp41	aa644-663	+ + +
98-6	SZ	Human	Ibid, IgG2 Ab	gp41	aa644-663	+ +
167-7	SZ	Human	Ibid, IgG1 Ab	gp41	aa644-663	+
50-69 120-16 126-6 181-D 246-D	SZ	Human	Ibid, IgG Ab	gp41	Not to aa644-663 or aa603-609	NIL
MT-B22	ND	Human	Ibid, IgG Ab	gp120	NIL	NIL

*One of several murine and rat antibodies that bind to both HIV-1 gp41 and astrocytes.

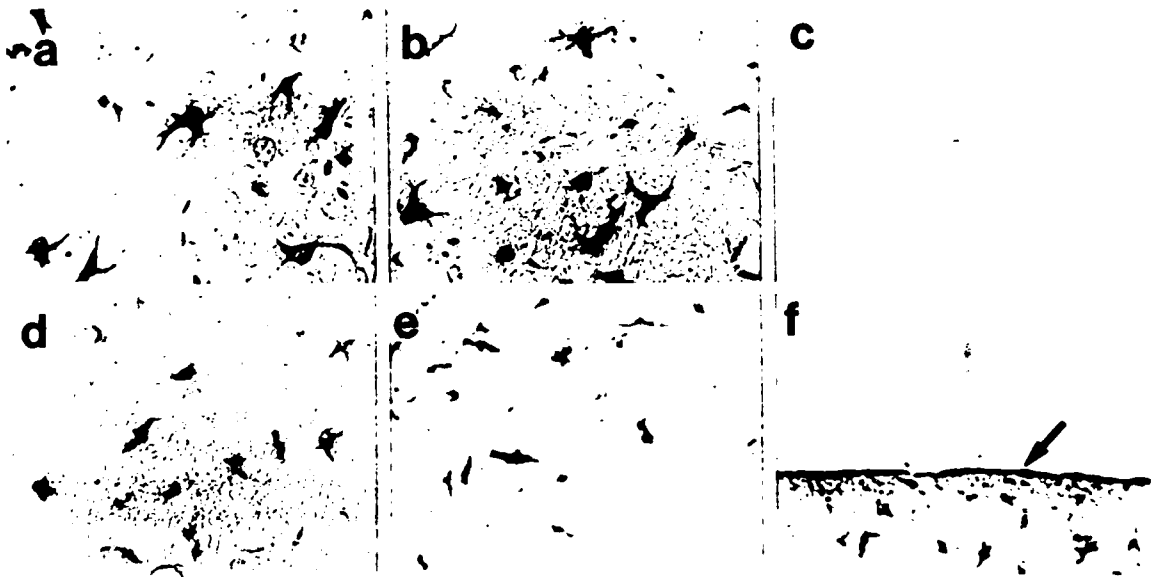


Figure 1

Figure 1 shows staining of reactive astrocytes in brain sections from scrapie-infected mice by cross-reactive anti-HIV-1 gp41 antibodies. Strong staining was seen with ND-15G1 and weaker staining with SZ-98.6 and SZ-167.7. Mouse mAb M22 was used as a positive control, and SZ-120.16, which did not stain reactive astrocytes, was a negative control. The *glia limitans* (arrow) was consistently stained by the cross-reactive antibodies (f). Key: a, mouse monoclonal M22; b, hu mAb ND-15G1; c, hu mAb SZ-120.16; d & f, hu mAb SZ-98.6; and e, hu mAb SZ-167.7.

Mapping of these three monoclonal antibodies' specificity using HIV-1 gp41 peptides located their epitopes to aa644-663 and established their conformation dependence.

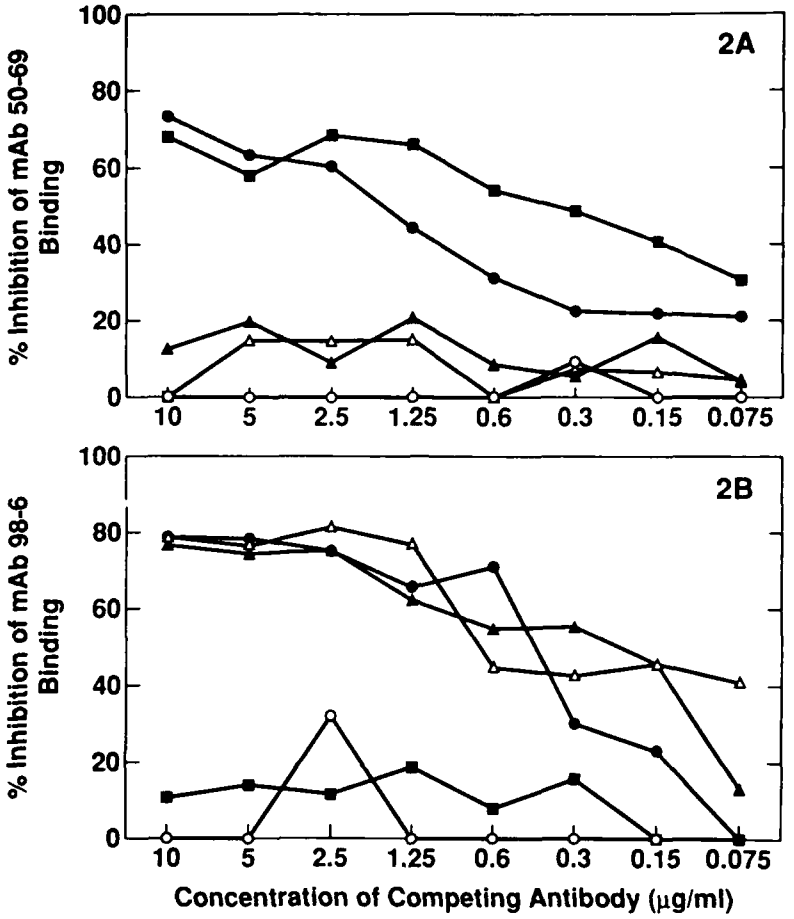


Figure 2A & 2B

Figure 2A & 2B shows the competition assays for inhibition of binding of human mAbs to whole HIV-1 lysate. Key: SZ-50.69, SZ-98.6, ND-15G1, HIV^+ serum, control serum.

A) ND-15G1 did not inhibit the binding of the immunodominant region 1-reactive mAb SZ-50.69 to HIV lysates. In contrast, both HIV^+ serum and SZ-50.69 itself effectively competed with labeled SZ-50.69.

B) ND-15G1 inhibited the binding of the immunodominant region 2-reactive mAb SZ-98.6 to HIV lysates. HIV^+ serum and the mAb SZ-98.6 also competed with the labeled antibody, but neither SZ-50.69 nor control HIV^- serum inhibited SZ-98.6 binding.

The six other human monoclonal antibodies to HIV-1 (Table 1) bound to gp41 or gp120 but not to reactive astrocytes in brain tissue.

The sharing of linear or conformational protein determinants is termed molecular mimicry (see M.B.A. Oldstone, Molecular Mimicry and Disease. *Cell* 50:819-820, 1987). The consequences of such mimicry by antibodies to HIV interacting with astrocytes may play a role in the dementia of AIDS patients since a major function of astrocytes is to maintain the appropriate milieu for neuronal function. The finding of such cross-reactive antibodies adds to the evidence of a possible autoimmune pathogenesis for some of the disease manifestations accompanying HIV infection. For anti-astrocyte antibodies to disturb CNS function they must be present within the brain parenchyma during disease. This could occur via the extravasation of antibodies directly from serum into the brain and/or the intrathecal production of antibodies by B cells present within the CNS. Reactive astrocytosis is an early consequence of HIV infection of the CNS, occurring prior to clinical manifestation of disease. We noted that astrocyte expression of the cross-reactive epitope was widespread in the CNS during astrocytosis, particularly on endfeet forming the *glia limitans*. Astrocytes' endfeet are in intimate contact with blood vessels and would come into contact with extravasating antibody.

b) Attempts to Isolate the Astrocyte Gene that Encodes the 43kD Astrocytic Protein that Binds to Monoclonal Antibodies Raised Against the HIV-1 GP41 Immunodominant Domain and Studies of Tissue Factor (TF) in Astrocytes

Three libraries were constructed that had high expression of the 43kD astrocytic protein. One library was created from brains of mice infected with Theiler's virus, a second from brains of mice infected with scrapie agent and a third from scrapie-infected mouse hippocampus. Although several suggestive positive colonies were detected using mouse antibodies to HIV-1 gp41, none enriched or amplified. Approximately 5 x 10^6 plaques were screened from each library. While concurrently we could select and amplify out other astrocyte specific genes, i.e., the gene encoding for glial fibrillary acidic protein, we were unsuccessful in obtaining the gene encoding the novel astrocyte 43kD protein.

However, while studying and manipulating astrocytes for the above cloning studies we serendipitously noted that astrocytes are the primary source of TF in the CNS. Analysis of murine brain sections by in situ hybridization demonstrated high levels of TF mRNA in cells that expressed glial fibrillary acidic protein.

For Figure 3 -- See next page

Figure 3 shows that TF mRNA is expressed in astrocytes. Three μm thick scrapie-infected mouse brain sections were sequentially hybridized with a ^{35}S-labeled anti-sense mouse TF riboprobes and then reacted with polyclonal anti-GFAP antibodies to identify astrocytes. TF mRNA-positive cells expressed GFAP (A-D) indicating that they were astrocytes. The GFAP positive *glia limitans* lining the brain (arrow, E,F) is negative for TF mRNA expression because of the lack of astrocyte cell bodies in this limiting boundary. In contrast, the overlying *arachnoid mater* (arrowhead, E,F) is strongly positive. Positive hybridization signals appear as black grains (A,C,E,F) or as blue-green grains using polarized light epiluminescence (B,D). The brown precipitate identifies astrocyte cell bodies and structures containing GFAP. Magnification is either x400 (A,B,E) or x1000 (C,D,F).

In addition, primary astrocyte cultures and astrocyte cell lines from mouse, rat and human constitutively express TF mRNA and functional protein.

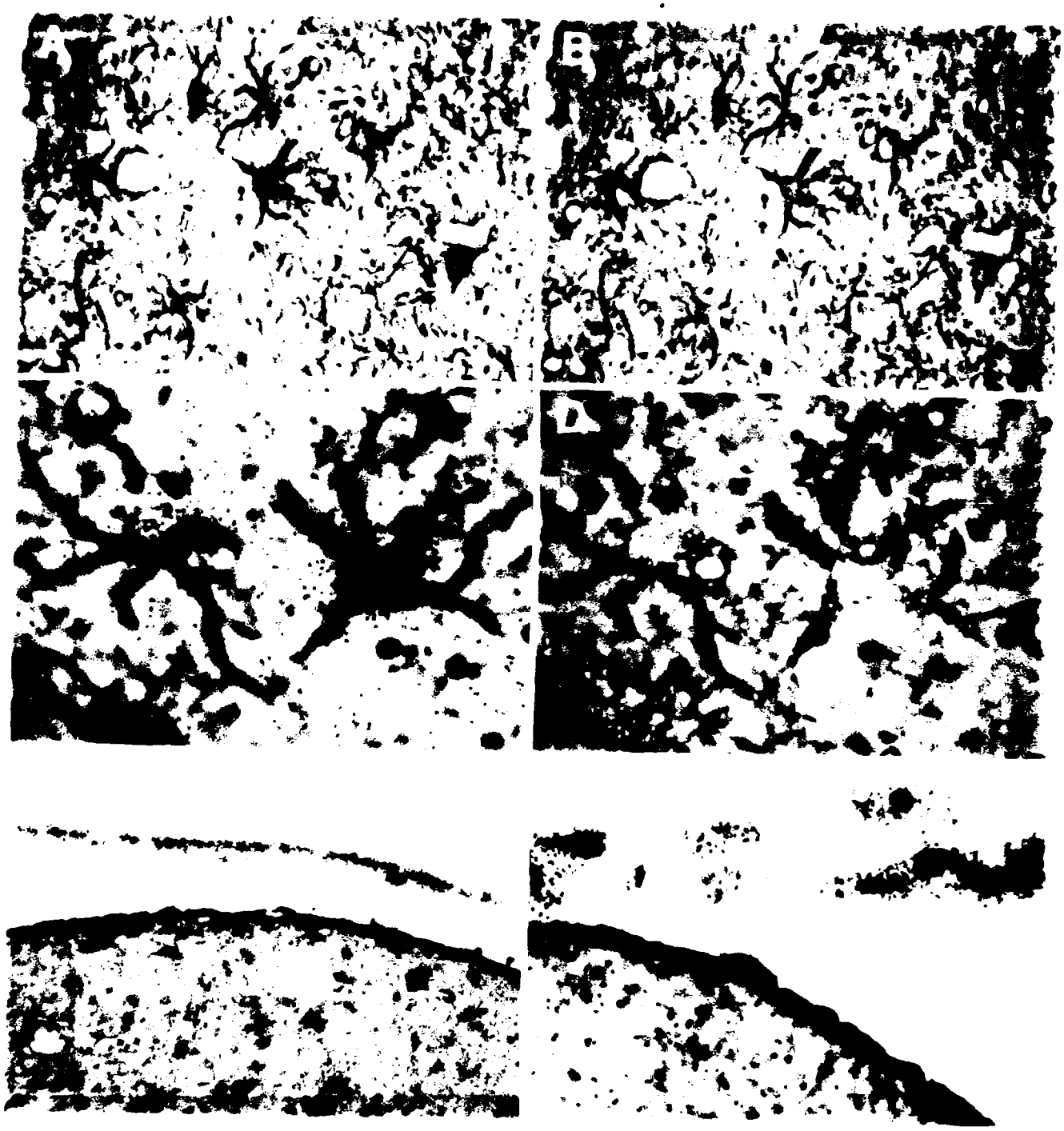


Figure 3

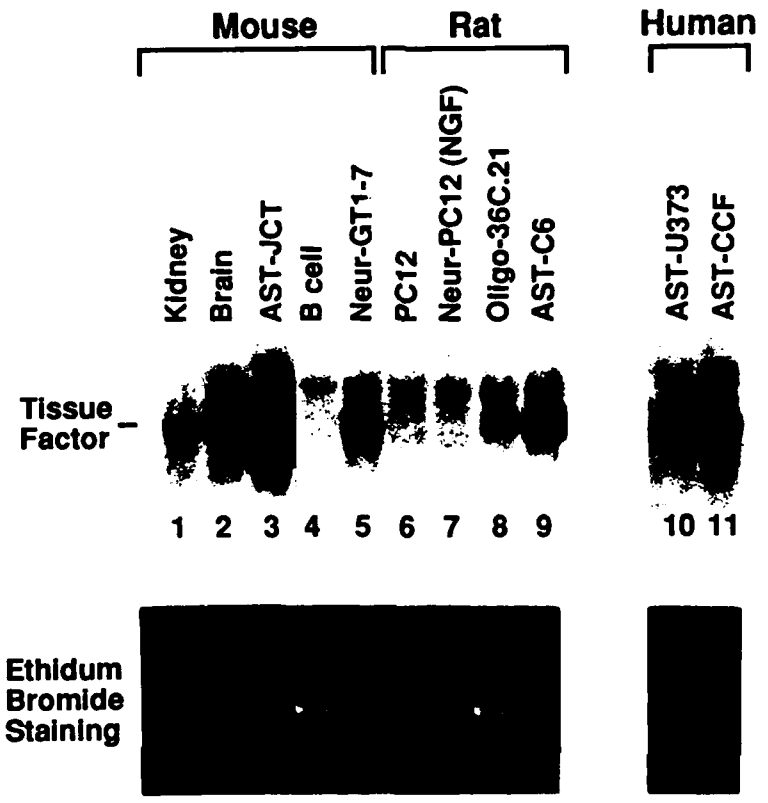


Figure 4

Figure 4 shows TF is expressed in astrocyte cell lines of various species. Total RNA was isolated from mouse kidney and brain, the murine astrocyte cell line JCT, the rat glioma cell line C6, two human astrocytic cell lines U373 MG and CCF-STTGI, the rat oligodendrocyte cell line 36C.21, the mouse neuronal cell line GT1-7, rat PC12 cells both undifferentiated, and differentiated with βNGF, and as a negative control the BALB/c mouse myeloma B cell line J558L. Ten μg of each RNA was resolved on a formaldehyde denaturing gel, transferred to a nylon membrane and hybridized sequentially to ^{32}P-labeled murine and human TF cDNA probes. This was required because under the stringent conditions used the mouse TF probe did not cross-hybridize with the human TF mRNA. The membrane was washed at high stringency (0.2x SSC, 60°C) and exposed overnight to autoradiography. Various housekeeping genes utilized (GAPDH, CHO-B & β-actin) all varied in their expression between the different cells lines and species. Therefore, the original ethidium bromide staining of the gel was used to indicate RNA loading.

c) Analysis of CTL Activity in HIV-1 Infected Individuals

We established procedures to recover active CTL from peripheral blood mononuclear cells (PBMM) collected several years earlier and stored in liquid nitrogen. Figure 5 shows a typical CTL assay. Panel A is the data on MHC-restricted targets, Panel B on allogeneic targets, and Panel C for NK cell activity. Observe Panel A and note high CTL response to ENV over a wide-dose response, significant response to GAG, negligible response to NEF and TAT. Note the controls of uninfected cells (uninf) and vaccinia virus recombinant expressing β-galactosidase (β-GAL). Note in Panel B the absence of response in allogeneic cells infected with vaccinia virus expressing ENV or GAG with the patient's same CTL and assay run at the same time.

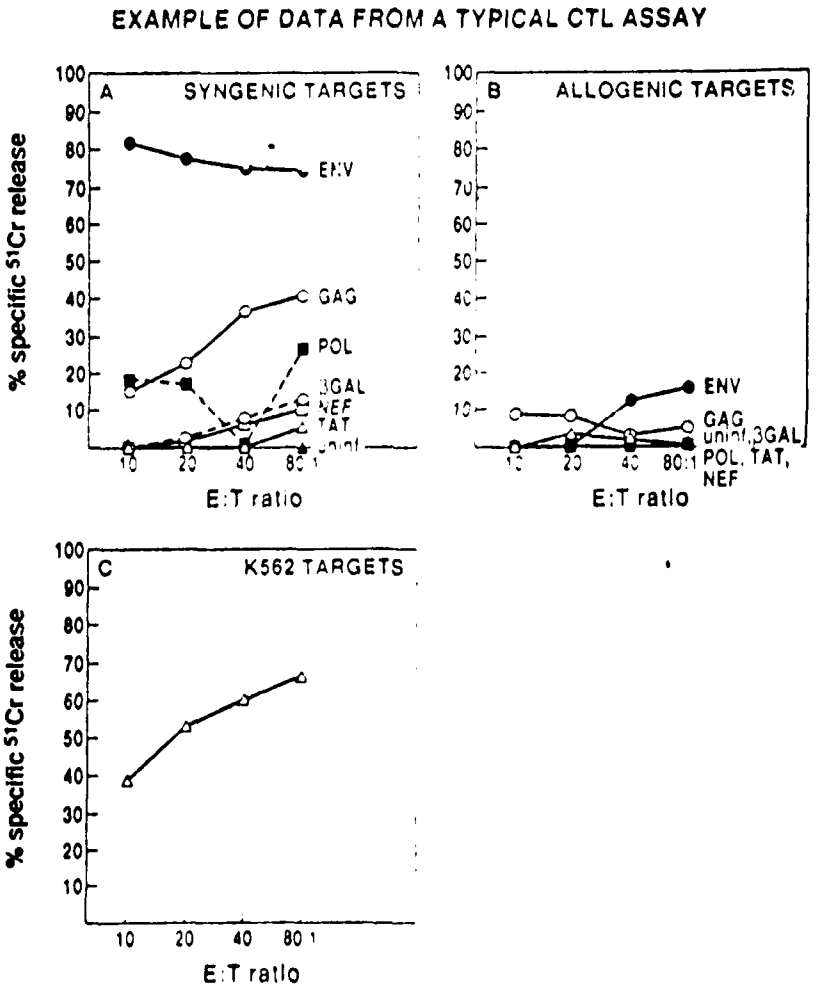
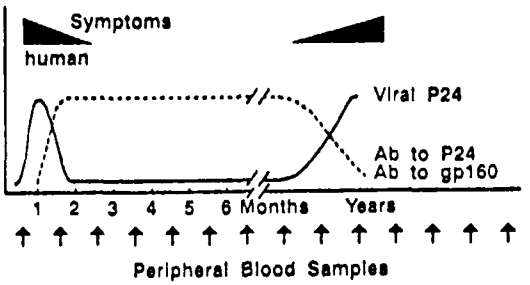


FIGURE 5

CTL activity was HLA Class 1 restricted and dependent on $CD8^+$ cells as determined by 1) use of HLA Class 1 transfected cells and 2) CD4 and CD8 antibody depletion studies.

Four patients, SUMA, INME, WEAU and BORI were studied using the format shown in Figure 6 along the patient's own B cells transformed with EBV and infected with vaccinia virus expressing either HIV-1 envelope (ENV), GAG, polymerase (POL), NEF or beta galactosidase (negative control). In addition, a number of peptides were synthesized (see Figure 6) and used to coat uninfected target cells.



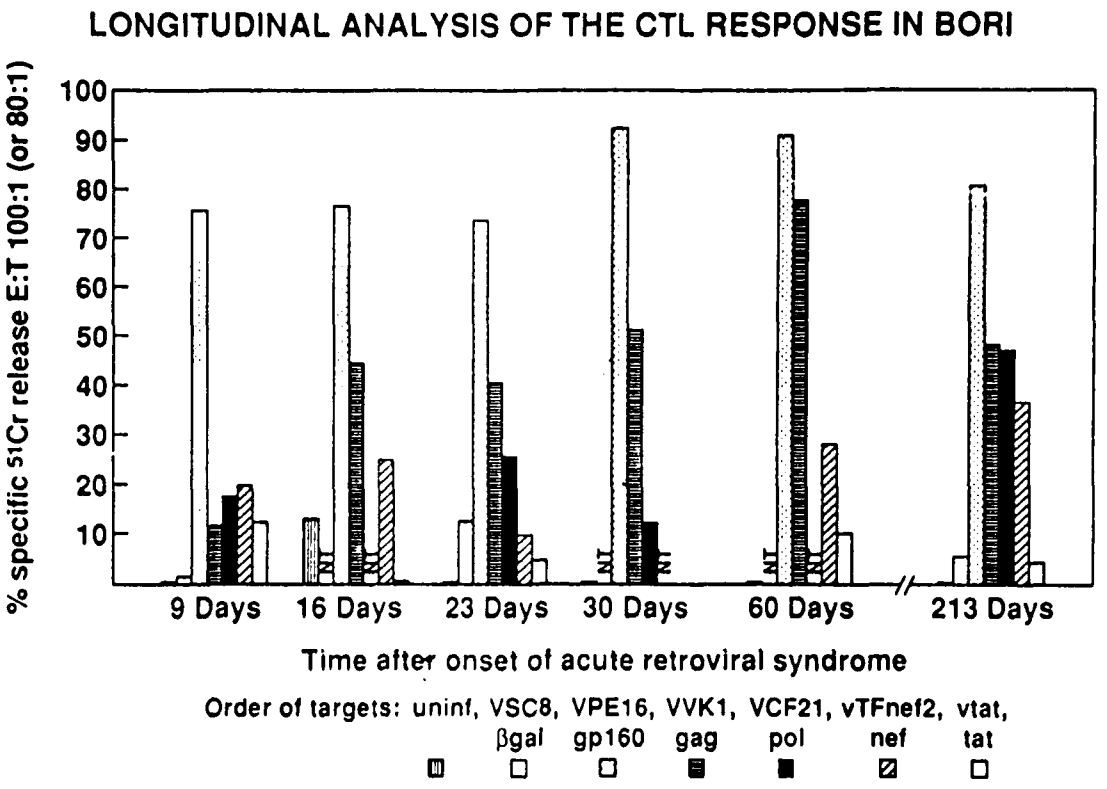
Patient	HLA A	HLA B	Peptides (GAG)
SUMA	11, 24	14, 62	B14 293-404
			185-199
INME	1, 29	8, 45	120-130
			305-313
WEAU	1, 29	8, 44	B8 21-33
			255-269
BOR1	2, 29	14, 44	325-339
			A2 71-85
			193-203
			219-233
			418-433

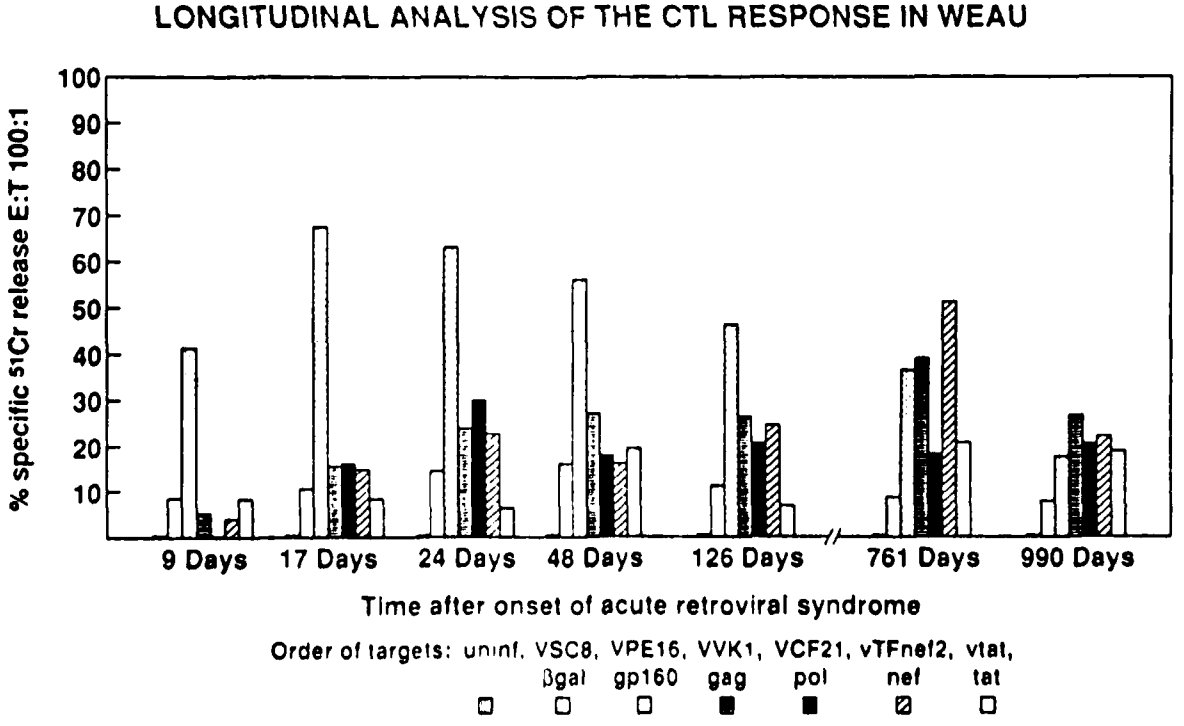
Figure 6

Longitudinal analyses of CTL activity for BORI and WEAU are near completion while data for SUMA and INME is partially completed and ongoing.

For Figures 7 & 8 -- See next page

Figures 7 & 8 show CTL kinetics during the course of infection from BORI (Figure 7) and WEAU (Figure 8). Compare these responses to changes in viral load and viral clearance on same patients reported by Dr. Shaw's group (Piatak *et al.*, *Science* 259:1749-1754, 1993). These two patients are of interest because of decrease in CTL activity, increased viral load, and the development of disease (WEAU), or lack of decrease in CTL activity (BORI). Also note the highest CTL response is to ENV, not GAG, as frequently stated in the literature.


LONGITUDINAL ANALYSIS OF THE CTL RESPONSE IN BORI
% specific 51Cr release E:T 100:1 (or 80:1)
100
90
80
70
60
50
40
30
20
10
NT
9 Days
16 Days
23 Days
30 Days
60 Days
213 Days
Time after onset of acute retroviral syndrome
Order of targets: uninf, VSC8, VPE16, VVK1, VCF21, vTFnef2, vtat,
βgal gp160 gag pol nef tat


LONGITUDINAL ANALYSIS OF THE CTL RESPONSE IN WEAU
% specific 51Cr release E:T 100:1
100
90
80
70
60
50
40
30
20
10
9 Days
17 Days
24 Days
48 Days
126 Days
761 Days
990 Days
Time after onset of acute retroviral syndrome
Order of targets: uninf, VSC8, VPE16, VVK1, VCF21, vTFnef2, vtat,
βgal gp160 gag pol nef tat

Figures 7 & 8

CTL ENV epitope for BORI (HLA B-14 restricted) has been mapped and is located in gp120.

Table 2

		% Specific ^{51}Chromiun Released from				
		BORI B Lymphocytes			Allo B Lymphocytes	
Peptide used to coat targets	E.T. Ratio:	50:1	25:1	12.5:1	50:1	25:1
AVERYLKDQQL		46	41	33	7	6
ERYLKDQQL		55	54	42	12	10
Vaccinia virus expressing						
gp160		74	72	69	16	14
gp120		27	51	49	5	2
beta galactosidase		2	2	1	2	2

ENV gene from BORI and WEAU is currently being manipulated to produce minigenes that express 110-120aa. These minigenes are being inserted into transfer vectors and then recombined with vaccinia virus. These reagents will be used in the future to map all the ENV epitopes.

Similar GAG minigenes expressing 350 to 400 amino acids have now been successfully placed in a shuttle vector and will be recombined with vaccinia.

III. Summary of the Final Scientific Report

Three monoclonal antibodies to gp41 aa644-663 occurring in three HIV-1$^+$ individuals bind to a novel astrocytic antigen found in mammalian brains. An astrocyte gene encoding this novel antigen was not obtained. Astrocytes were noted to be the major (only?) source of tissue factor (TF) in the CNS. Further, TF mRNA which is constitutively expressed was noted to be markedly enhanced in certain persistent viral infections. CTL activity was kinetically followed in four selected patients from the early onset of infection over their clinical course. CTL activity to ENV occurs early and associates with the initial clearance of virus. The association of CTL activity late in disease when clinical AIDS occurs and the presence or absence of how CTL escape HIV variants is under current analysis. Three CTL epitopes for HIV were uncovered. One in this report and the two others are noted in the Mid-Term Report.

PUBLICATIONS:

Oldstone, M.B.A. Molecular mimicry as a mechanism for the cause and as a probe uncovering etiologic agent(s) of autoimmune disease. Curr. Topics Microbiol. Immunol. 145:127-135, 1989.

Gnann, J.W., L.L. Smith and M.B.A. Oldstone. Custom-designed synthetic peptide immunoassays for distinguishing HIV type 1 and type 2 infections. In: Methods in Enzymology: Immunochemical Techniques -- Anti-idiotypic Antibodies and Molecular Mimicry, Langone J.L. (ed.), Academic Press, Orlando, FL, Vol. 178, pp. 693-714, 1989.

Gnann, J.W. and M.B.A. Oldstone. Using synthetic peptide reagents to distinguish infections caused by different HIV strains. Curr. Topics Microbiol. Immunol. 160:131-143, 1990.

Oldstone, M.B.A. Molecular basis of viral persistence. In Human Retrovirology: HTLV, W.A. Blattner, ed., Raven Press, Inc., N.Y., 1990, pp. 27-34.

Oldstone, M.B.A., A. Tishon, H. Lewicki, H.J. Dyson, V.A. Feher, N. Assa-Munt and P.E. Wright. Mapping the anatomy of the immunodominant domain of the human immunodeficiency virus gp41 transmembrane protein: Peptide conformation analysis using monoclonal antibodies and proton nuclear magnetic resonance spectroscopy. J. Virol. 65:1727-1734, 1991.

Yamada, M., A. Zurbriggen, M.B.A. Oldstone and R.S. Fujinami. Common immunologic determinant between human immunodeficiency virus type 1 gp41 an astrocytes. J. Virol. 65:1370-1376, 1991.

Littaua, R.A., M.B.A. Oldstone, A. Takeda, C. Debouck, J.T. Wong, C.U. Tuazon, B. Moss, F. Kievets and F.A. Ennis. An HLA-C-restricted CD8+ cytotoxic T-lymphocyte clone recognizes a highly conserved epitope on human immunodeficiency virus type 1 gag. J. Virol. 65:4051-4056, 1991.

Tishon, A., A. Salmi, R. Ahmed and M.B.A. Oldstone. Role of viral strains and host genes in determining levels of immune complexes in a model system: Implications for HIV infection. AIDS Res. & Human Retroviruses, 7:963-969, 1991.

Littaua, R.A., M.B.A. Oldstone, A. Takeda and F.A. Ennis. A CD4+ cytotoxic T-lymphocyte clone to a conserved epitope on human immunodeficiency virus type 1 p24: Cytotoxic activity and secretion of interleukin-2 and interleukin-6. J. Virol. 66:608-611, 1992.

Oldstone, M.B.A. Molecular anatomy of viral persistence. J. Virol., 65:6381-6386, 1991.

Mucke, L. and M. Eddleston. Astrocytes in infectious and immune-mediated diseases of the central nervous system. FASEB J., in press, 1993.

Eddleston, M., J.C. de la Torre, M.B.A. Oldstone, D.J. Loskutoff, T.S. Edgington and N. Mackman. Astrocytes are the primary source of tissue factor in the murine central nervous system -- A role for astrocytes in cerebral hemostasis. J. Clin. Invest., in press, 1993.

Eddleston, M., J.C. de la torre, J.-Y. Xu, N. Dorfman, A. Notkins, S. Zolla-Pazner and M.B.A. Oldstone. Molecular mimicry accompanying HIV-1 infection -- human monoclonal antibodies that bind to gp41 and to astrocytes. AIDS Res. Human Retro., in press, 1993.

Eddleston, M. and L. Mucke. Molecular profile of reactive astrocytes -- implications for their role in neurologic disease. Neuroscience 54:15-36, 1993.

Oldstone, M.B.A. Viruses and diseases of the twenty-first century. Rous-Whipple Award Lecture, Amer. J. Pathol., in press, 1993.

Oldstone, M.B.A. and G.F. Rall. Mechanism and consequence of viral persistence in cells of the immune system and neurons. Intervirology, in press, 1993.

Oldstone, M.B.A. HIV-neurons and cytotoxic T lymphocytes: Concepts about the AIDS dementia complex and viral persistence. Assoc. for Res. in Nervous and Mental Disease Mtg. (ARNMD), in press, 1993.

ABSTRACTS:

Schrier, R.D., J. W. Gnann, Jr., R. Landes, C. Lockshin, D. Richman, A. McCutchan, C. Kennedy and M.B.A. Oldstone. T cell recognition of HIV peptides. Universitywide Task Force on AIDS, San Diego, March 1989.

Littaua, R.A., M.B.A. Oldstone, A. Takeda, C. Tuazon, F. Kievits and F.A. Ennis. A highly conserved epitope on HIV-1 GAG recognized by an HLA-C restricted $CD8^+$ CTL clones. Seventh International Conference on AIDS, Florence, Italy, June 1991.

Eddleston, M., A. Tishon, C.F. Evans, J.L. Whitton and M.B.A. Oldstone. Vaccination to prevent persistent infection. American Society for Virology, Cornell University, Ithaca, New York, 11-15 July 1992.

Eddleston, M.P., J.C. de la Torre, M.B.A. Oldstone and N. Mackman. Tissue factor expression in astrocytes in vitro and in vivo. Society for Neuroscience, Anaheim, CA, 25-30 October 1992.

Oldstone, M.B.A. The anatomy of viral persistence. ARNMD Symposium on HIV, AIDS and the Brain, New York, 4 December 1992.

Eddleston, M.P., N. Mackman, J.C. de la Torre and M.B.A. Oldstone. Coagulation factors in the CNS: Expression and significance of tissue factor. Amer. Assoc. of Neuropathologists, Salt Lake City, Utah, 9-13 June 1993.

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RESULTING GRADUATE DEGREES

Michael Eddleston expects to receive his graduate degree in 1994